27
20. (New) The set of oligonucleotide probes of claim 4, wherein the designate nucleotides and/or nucleotide analogs comprise a purine or pyrimidine base, a ribose or deoxyribose sugar, and a phosphate group.

28 21. (New) The set of oligonucleotide probes of claim 7, wherein the designate nucleotides and/or nucleotide analogs comprise a purine or pyrimidine base, a ribose or deoxyribose sugar, and a phosphate group.

29 22. (New) The array of claim 8, wherein the designate nucleotides and/or nucleotide analogs comprise a purine or pyrimidine base, a ribose or deoxyribose sugar, and a phosphate group.

30 23. (New) A set of oligonucleotide probes, comprising a plurality of instances of a sequence of universal and designate nucleotides and/or nucleotide analogs, wherein

(a) the universal and designate nucleotides and/or nucleotide analogs are ordered in a pattern,

(b) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(c) the first string and the second string each comprise a universal nucleotide and/or nucleotide analog, and

(d) the first segment and the second segment each comprise a designate nucleotide.

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REMARKS

General Remarks

Applicants note with appreciation the Examiner's decision to rejoin claims 1-12 for examination, and the Examiner's acknowledgement of the priority claims.

Claims 1-12 are pending in this application; claims 1, 4, and 6-12 have been amended, claim 5 has been canceled and new claims 13-23 have been added. Support for these

amendments and the newly added claims may be found generally throughout the specification and claims as originally filed. With respect to claims 1, 13, 18, 23, and claims depending therefrom, support may be found, for example, at page 4, lines 13-30 and at page 13, middle paragraph. With respect to claims 4, 6-12, 16, 17 and 20-22 support may be found, for example, at page 11, lines 19-28 and page 12, lines 4-19. With respect to the term "array", as amended into claims 7-12, exemplary support for this term may be found at page 14, lines 18-26.

Accordingly, no new matter has been added.

In amending or canceling claims, Applicants reserve the right to pursue the claims as filed or claims of differing scope in this or future applications.

Applicants address below the issues raised by the Examiner.

DRAWINGS:

The Examiner has objected to the drawings, suggesting that Figures 5 and 10 are impossible to read and that Figures 7 and 8 are "Prior Art".

Applicants are filing herewith a Letter to the Official Draftsperson, including substitute informal drawings for Figures 5, 9 and 10 and marked up copies showing changes. These changes are intended to improve the legibility of the text on the Figures. Applicants contend that the identity of the data lines on each of the graphs is sufficiently clear from the labeling that it is unnecessary to render the lines themselves in distinguishably different formats.

Applicants wish to delete Figures 7 and 8. The specification is amended accordingly, and Figures 9 and 10 are renumbered as 7 and 8 respectively.

SEQUENCE LISTING:

The Examiner has requested a Sequence Listing.

Applicants provide herewith paper and computer readable forms of the Sequence Listing, as required by 37 CFR 1.821 - 1.825. Applicants request entry of the sequence listing into the application. The sequences in the listing are identical to those presented in the Figures as originally filed. In addition, amendments are submitted to insert references to SEQ ID NO:1 and

SEQ ID NO:2 in the specification. Applicants note that the subject sequences are exemplary and are provided in the application solely for illustrative purposes.

CLAIM OBJECTIONS:

The Examiner has objected to the phrase "comprising sequence" in claim 1. This phrase has been changed to "comprising a sequence" as recommended by the Examiner. Applicants request withdrawal of this objection.

CLAIMS 4-6, AND 10 REJECTED UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner alleges:

> Claims 4-6, and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.
>
> In claims 4 and 5, is it the probes that are in an iterative pattern, or is it the universal and designate nucleotides within each probe that are in an iterative pattern?
>
> Claim 10 is drawn to a chip of claim 8 "having a universal nucleotide..." Claim 6 similarly recites a set of probes "having a universal nucleotide...". This is confusing, as it is not clear whether there is only one universal nucleotide in the whole chip or set, or whether each probe must comprise at least one universal nucleotide.

The Examiner is respectfully reminded that all that is required by the second paragraph of section 112 is that the claims set out and circumscribe particular subject matter that the Applicant regards as the invention with a reasonable degree of precision and particularity. See In re Borkowski, 164 U.S.P.Q. 642 (C.C.P.A. 1970).

The Federal Circuit has emphasized that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, for example, In re Marosi, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983).

According to the Federal Circuit, whether a claim is invalid under the second paragraph of Section 112 requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification.

With respect to claims 4 and 5, when read in light of the specification by one of skill in the art it would be understood that at least the universal and designate nucleotides and/or nucleotide analogs are ordered in a pattern. Nevertheless, as suggested by the Examiner, the claims have been amended to clarify this issue. It should be noted that the claims as amended do not specify whether the probes as a group are arranged in a pattern, and accordingly the claims encompass the appropriate probe sets regardless of whether the probes as a group are arranged in a pattern or not.

With respect to claim 10 and claim 6, the claims have been amended to recite "universal nucleotides", thus clarifying the issue.

Applicants request reconsideration and withdrawal of these rejections under 35 U.S.C. 112, second paragraph.

CLAIM 1-12 REJECTED UNDER 35 U.S.C. 102

The Examiner contends that claims 1-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Mirzabekov et al. (US 5,908, 745).

> The above rejected claims are drawn to isolated polynucleotides comprising designate and universal bases in an iterative pattern...Mirzabekov et al. (5,908,745) disclose isolated polynucleotides which comprise both designate and universal bases in iterative patterns. These polynucleotides can be displayed on a chip and used for sequencing. An example of the iterative pattern of Mirzabekov et al. is set forth at column 5, lines 30-61, and in claims 17 and 19.

Applicants respectfully disagree with the Examiner's interpretation of Mirzabekov. At column 5, lines 30-61, Mirzabekov merely teaches pentamer probes composed entirely of universal nucleotides with the exception of a single designate position, such as N-A-N-N-N or A-N-N-N-N, where "N" represents a universal nucleotide. Applicants were unable to find any other description of probes having universal nucleotides in Mirzabekov. It is Applicants'

position that these sequences disclosed by Mirzabekov are not iterative, and accordingly, Mirzabekov does not meet the elements claims 1-3 and 5 as filed.

In addition, Applicants note that Mirzabekov is a method solely for identifying nucleotide polymorphisms in the context of an otherwise known sequence. For example, at column 3, lines 9-15, Mirzabekov states:

> In brief, the objects and advantages of the present invention are achieved by a method for detecting disease associated alleles in patient genetic material comprising immobilizing a first group of oligonucleotide molecules of a predetermined length on a predetermined position on a substrate, said oligonucleotide molecules synthesized to compliment (*sic*) base sequences of the disease associated alleles...

The methods of Mirzabekov are not suitable for generating a sequence de novo. The oligonucleotides taught by Mirzabekov are therefore designed for the detection of single base pair changes in the context of a known sequence. While the methods and compositions of the present invention are suited for detection of mutations, they are also, among other things, suited for de novo sequencing.

Nonetheless, with respect to claims 1 and 4 and their dependents, claims 1 and 4 are amended solely to expedite prosecution. Claims 1 and 4 as amended recite patterns of designate and universal nucleotides that are not taught by Mirzabekov. Applicants further contend that the teachings of Mirzabekov are insufficient to lead one of skill in the art to design oligonucleotides having such patterns.

With respect to claims 7 -12, Applicants note that Mirzabekov teaches the use of probes having universal nucleotides only in the mobile phase, and not displayed on a solid substrate. See, for example, column 5, lines 9-12, "The first hybridization is conducted with the 200 overlapping immobilized oligomers, as discussed supra, to pin-point the region where DNA changes exist. Then hybridization with the 1,024 *mobile* pentamers is conducted." (*emphasis added*). Accordingly, Mirzabekov does not teach probes of the invention displayed or disposed on a solid substrate, and therefore Mirzabekov does not anticipate claims 7-12. In addition, Applicants note that the methods of Mirzabekov depend on using the pentamers, in mobile form, in a second round of hybridization. Therefore, the teachings of Mirzabekov would not teach or motivate one of skill in the art to display such probes on a solid substrate.

Finally, Applicants disagree with Examiner's statement that some sets of probes comprise at least two fixed positions at an end. Applicants see no mention of such probes.

Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. 102(e).

The Examiner further argues:

> Claims 1 and 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 90/04652... WO 90/04652 discloses oligonucleotides which have both designate (fixed) and universal (non-fixed) bases, in an iterative pattern (See pages 4-6 and Figure 1). A preferred universal base is deoxyinosine. Some of the oligonucleotides disclosed have two fixed positions at the end of the oligonucleotides.

Applicants respectfully assert that WO 90/04652 does not anticipate the subject claims. Applicants maintain that the term "non-fixed" of WO 90/04652, which is symbolically represented as "0", is not the same as the term "universal" as used in the present application. For example, at page 4, WO 90/04652 teaches, "(T)he above notation will be simplified to AA00A00A, where A represents deoxyadenosine and 0 represents *the absence of deoxyadenosine.*" (*emphasis added*). The "non-fixed" position is shown as being occupied by any base that does not hybridize with "T". Applicants note that the term "universal" as used in the subject claims is used to refer to an entity (or collection of entities mutually substituted at a position) that is relatively non-specific with respect to all of A, T, C and G. Exemplary universal bases are 5-nitroindole and 3-nitropyrrole. As would be appreciated by one of skill in the art, any "universal" base will have some heterogeneity in free energy of hybridization with different partners, but a "universal" base is not intended to be equated to a "non-fixed" base of WO 90/04652 that hybridizes specifically to any three of A, T, C and G but fails to hybridize meaningfully to the fourth. The "non-specific" base of WO 90/04652 is intended to have a very selective lack of hybridization to one of the four natural bases. Therefore, Applicants assert that WO 90/04652 does not anticipate any pending claim, either as filed or as amended.

Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. 102(b).

In addition, the Examiner contends that:

> Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Loakes et al. (1995). Loakes et al...disclose polynucleotide probes which comprise universal and designate bases in iterative patterns. Table 1 shows examples of these patterns, especially probes 2, 6 and 9. These probes also have two fixed bases at the end of the probe - "CC". Therefore the disclosure of Loakes et al. meets the limitations of the rejected claims.

Applicants note at the outset that Loakes et al. teaches such probes only in the context of Sanger sequencing and PCR experiments. For example, in column 2 of page 2361, Loakes states, "To be of routine use in recombinant DNA experiments the modified oilgonucleotides *must be able to* prime DNA polymerases." (*emphasis added*). As a result, Loakes does not teach or suggest generating a set of probes having more than one instance of a pattern. For example, all of the probes presented in Table 1 of Loakes are based on and intended to replace the single designated oligonucleotide sequence (i.e. single instance) presented at the top of the table. There is no suggestion that it would be useful to create any alternative instances. Accordingly, Applicants maintain that Loakes does not anticipate claims 4-6 drawn to sets of nucleic acid or oligonucleotide probes.

In addition, with respect to claim 1 and its dependents, claim 1 has been amended solely to expedite prosecution. As amended, claim 1 recites patterns that are not taught in Loakes. Moreover, Loakes provides no motivation to create such patterns.

Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. 102(b).

Finally, the Examiner argues that claims 1-3 are anticipated by Bergstrom et al. (US 5,681,947).

The Examiner states:

> Bergstrom et al. disclose oligonucleotides of at least 10 bases, wherein they comprise at least one universal base...Table 1, primer 72 discloses the oligonucleotide which has 3-nitropyrrole in an iterative pattern, and has two designated bases at either end. Therefore, the disclosure of Bergstrom et al. meets the limitations of the rejected claims.

Applicants note that, as a whole, Bergstrom does not teach or suggest the use of such probes for sequencing by hybridization. Nonetheless, as noted above, claim 1 has been amended

solely to expedite prosecution. As amended, claim 1 recites patterns that are not taught or suggested in Bergstrom.

Accordingly, Applicants request reconsideration and withdrawal of this rejection under 35 U.S.C. 102(b).

AMENDMENTS SHOWN WITH BRACKETS AND UNDERLINES:

**In the Specification:**

Page 6, replace the paragraph beginning "Fig. 2" at line 10 is amended as follows:

Fig. 2 presents sample spectra obtained using probes as described herein. The exemplary seventeen nucleotide nucleic acid sequence is SEQ ID NO:1.

Page 6, replace the paragraph beginning "Fig. 4" at line 13 is amended as follows:

Fig. 4 illustrates the evaluation of the spectrum for different extensions. The exemplary ten nucleotide nucleic acid sequence is SEQ ID NO:2.

At page 6, the paragraph beginning "Fig. 5" at line 14 is amended as follows:

Fig. 5 depicts test results comparing the sequencing of DNA using various probes as described herein with the sequencing of DNA using conventional probes. The bracketed number pairs, such as (4,5) represent the type of (s,r) probe set used. A (9,0) probe set is a conventional, or classical, probe set.

At page 6, the paragraph at line 20 beginning "Fig. 9" is amended as follows:

Fig. [9] 7 illustrates (a) Hamiltonian and (b) Eulerian paths in the graph associated with a given target sequence. Both paths provide ambiguous reconstructions. The seventeen nucleotide target sequence is SEQ ID NO:1.

Page 6, the paragraph at line 22 beginning "Fig. 10" is amended as follows:

Fig. [10] 8 depicts test results comparing the sequencing of random nucleotide sequences using various probes as described herein with sequencing using conventional probes. The

bracketed number pairs, such as (4,5) represent the type of (s,r) probe set used. A (9,0) probe set is a conventional, or classical, probe set.

Page 24, the paragraph beginning at line 33 and ending on page 25 is amended as follows:

One embodiment of the systems and methods described herein is a computer system configured to sequence a nucleotide sequence by analyzing a spectrum generated according to the systems and methods described herein, e.g., by executing a computer program in a computer language, e.g., Fortran, C, Java, etc., based upon the pseudocode of Table 1. [An embodiment of such a computer system is depicted in Figure 7.] In an additional embodiment, the systems and methods described herein relate to a disk, CD, or other permanent computer-readable storage medium that encodes a computer program capable of reconstructing a nucleotide sequence by analyzing a spectrum generated using gapped probes, such as a program based on the pseudocode of Table 1. [An exemplary disk 40 is depicted in Figure 8.]

**In the Claims:**

1. (Amended) A nucleic acid probe, comprising a sequence of universal and designate nucleotides ordered in [an iterative] a pattern, wherein

(a) the pattern comprises a first string of universal nucleotides followed by a first segment, and a second string of universal nucleotides followed by a second segment,

(b) the first string and the second string each comprise two or more consecutive universal nucleotides; and

(c) the first segment and the second segment each comprise a designate nucleotide.

2. The probe of claim 1, having a universal nucleotide selected from the group consisting of 5-nitroindole and 3-nitropyrrole.

3. The probe of claim 1, further comprising at least two contiguous designate nucleotides bound to an end of the sequence.

4. (Amended) A set of [nucleic acid] oligonucleotide probes, comprising a plurality of instances of a sequence of universal and designate nucleotides and/or nucleotide analogs, wherein the universal and designate nucleotides and/or nucleotide analogs are ordered in [a] an iterative pattern.

5. (Canceled).

6. (Amended) The set of [nucleic acid] oligonucleotide probes of claim 4, [comprising] wherein the [a] universal nucleotides and/or nucleotide analogs [nucleotide] are selected from the group consisting of 5-nitroindole and 3-nitropyrrole.

7. (Amended) A set of [nucleic acid] oligonucleotide probes, comprising a plurality of instances of a sequence of universal and designate nucleotides and/or nucleotide analogs ordered in a pattern, wherein the probes are displayed on a solid support.

8. (Amended) A sequencing array [chip], comprising

a substrate, and

a set of [nucleic acid] oligonucleotide probes disposed thereon, wherein each probe comprises an instance of a pattern of universal and designate nucleotides and/or nucleotide analogs such that the set comprises a plurality of instances of the pattern.

9. (Amended) The array [chip] of claim 8, wherein the pattern is iterative.

10. (Amended) The array [chip] of claim 8, [having a] wherein the universal nucleotides and/or nucleotide analogs [nucleotide] are selected from the group consisting of 5- nitroindole and 3-nitropyrrole.

11. (Amended) The array [chip] of claim 8, wherein each particular instance is associated with a particular location on the array [chip].

12. (Amended) The array [chip] of claim 8, wherein each probe further comprises a sequence of at least two contiguous designate nucleotides and/or nucleotide analogs bound to an end of the pattern.

13. (New) An oligonucleotide probe, comprising a sequence of universal and designate nucleotides and/or nucleotide analogs ordered in a pattern, wherein

(a) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs, followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(b) the first and second strings each comprise two or more consecutive universal nucleotides and/or nucleotide analogs, and

(c) the first and second segments comprise at least one designate nucleotide and or nucleotide analog.

14. (New) The probe of claim 13, having a universal nucleotide and/or nucleotide analog selected from the group consisting of 5- nitroindole and 3-nitropyrrole.

15. (New) The probe of claim 13, further comprising at least two contiguous designate nucleotides and/or nucleotide analogs bound to an end of the sequence.

16. (New) The probe of claim 13, wherein the universal and designate nucleotides and/or nucleotide analogs are linked by analogs of phosphodiester bonds.

17. (New) The probe of claim 13, wherein the universal and designate nucleotides and/or nucleotide analogs are peptide nucleic acids.

18. (New) An oligonucleotide probe, comprising a sequence of universal and designate nucleotides and/or nucleotide analogs ordered in a pattern, wherein the pattern comprises a root and an iterated unit, and wherein the length of the root is identical to the length of the iterated unit.

19. (New) An oligonucleotide probe of claim 14, wherein each iterated unit comprises a string of universal nucleotides and/or nucleotide analogs followed by one or more designate nucleotide and/or nucleotide analog.

20. (New) The set of oligonucleotide probes of claim 4, wherein the designate nucleotides and/or nucleotide analogs comprise a purine or pyrimidine base, a ribose or deoxyribose sugar, and a phosphate group.

21. (New) The set of oligonucleotide probes of claim 7, wherein the designate nucleotides and/or nucleotide analogs comprise a purine or pyrimidine base, a ribose or deoxyribose sugar, and a phosphate group.

22. (New) The array of claim 8, wherein the designate nucleotides and/or nucleotide analogs comprise a purine or pyrimidine base, a ribose or deoxyribose sugar, and a phosphate group.

23. (New) A set of oligonucleotide probes, comprising a plurality of instances of a sequence of universal and designate nucleotides and/or nucleotide analogs, wherein

(a) the universal and designate nucleotides and/or nucleotide analogs are ordered in a pattern,

(b) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(c) the first string and the second string each comprise a universal nucleotide and/or nucleotide analog, and

(d) the first segment and the second segment each comprise a designate nucleotide.

## Conclusion

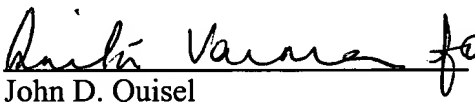
For the reasons given above, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims. Applicants submit that the pending claims, as amended, are in condition for allowance. If the Examiner believes that a personal or

telephonic interview would expedite allowance of these claims, he is invited to call the undersigned.

If there are any other fees, such as excess claims fees, due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
FOLEY, HOAG & ELIOT

August 23, 2001



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